REMARKS

Claims 8 and 10-18 are pending in the application, with claim 8 being amended and new claims 17 and 18 being added.

Rejection under 35 U.S.C. §103

The Examiner maintains the rejection of the claims as being obvious over Kondo et al., combined with Harada et al. and Shirakawa et al. In maintaining the rejection in the Advisory Action, the Examiner raises the following points each of which will be addressed in turn.

1) The Examiner acknowledges the references that were submitted to demonstrate the unpredictability in the field of the invention. However, the Examiner has only considered references that have publication dates after Harada et al. and Kondo et al. as probative. The Examiner's position is that work published prior to Kondo et al. and Harada et al. may not reflect the state of the art at the time of Harada et al. and Kondo et al. As a result the Examiner has not considered the probative value of Leithäuser et al. (1993) and Hiramatsu et al. (1994).

However, the work of Leithäuser et al. (1993) is cited in Harada et al. (1997) and Hiramatsu et al. (1994) is cited in both Harada et al. (1997) and Graham et al. (1998). Thus, even though Leithäuser et al. (1993) and Hiramatsu et al. (1994) pre-date the invention by approximately four years, the teachings reported in

Leithäuser et al. (1993) and Hiramatsu et al. (1994) were still accepted as the state of the art at the time of the invention in 1998. As such, the teachings of Leithäuser et al. (1993) and Hiramatsu et al. (1994) are probative evidence, which reflect the state of the art at the time of the invention and which support the arguments of pages 4-7 of the response of November 17, 2003. The Examiner is requested to reconsider the substantive teachings of these references and the arguments of November 17, 2003, particularly at pages 4-7.

2) The Examiner asserts that the findings of Graham et al. do not contradict those of Harada et al. The Examiner asserts that the only relevant teaching of Graham et al. is that PBC cells express Fas/CD95. The Examiner appears to fail to consider that the teaching in Harada et al. that Fas/CD95 is not found on normal liver and is up-regulated on PBC is contradictory to the report in Graham et al. that Fas/CD95 may be expressed on normal liver and there is no change with PBC cells. Applicants assert that the Examiner is incorrect in the position that the references are not contradictory.

Graham et al. teach that Fas is expressed on normal and pathological tissues and that there was no difference in the expression of Fas between pathological tissue and normal liver, whereas Harada et al. teach that Fas was not found on normal liver, but only expressed on pathological tissues as a high level. Thus,

the teachings of Graham et al. and Harada et al. are clearly different from each other. Specifically, Graham et al. states that since there was no change in the expression of Fas on pathological tissue compared to normal liver, "Fas-mediated mechanism is unlikely in view of expression we have seen." See page 556, lines 6-8. The conclusion is in opposite with the teachings of Harada et al. on page 1404, lines 21-12 from the bottom. Since the Graham et al. and Harada et al. teach different findings regarding the expression of Fas on normal and pathological tissues and concomitantly reach different conclusions, the teachings of Graham et al. and Harada et al. clearly would be considered contradictory to each other. The Examiner is requested to reconsider her position regarding these references.

3) In the final paragraph of page 2 of the Advisory Action, the Examiner takes that position that since chronic hepatitis leads to hepatic cirrhosis, the treatment of hepatitis will also result in hepatic cirrhosis. In reaching this conclusion, the Examiner has given the claims the broadest reasonable interpretation and the claims may be asserted to encompass the indirect treatment and prevention of hepatic cirrhosis through the treatment of chronic hepatitis. To address this point the claims have been amended to recite "and inhibiting apoptosis mediated by Fas" and to the treatment of hepatic cirrhosis. Harada et al. teach that the Fas expression was high and TUNEL index high on pathological tissues.

However, Harada et al. fails to actually demonstrate whether the apoptosis mediated by Fas is involved in the pathology. The involvement of Fas is only a presumption that Harada et al. reach based on their results. See page 1404, lines 21-12 from the bottom. On the other hand, as discussed above, Graham et al. reach the opposite conclusion and teach that apoptosis is unlikely to be a suitable therapeutic target for treating PBC. See the final sentence of page 556. Graham et al. further state that it had been reported that apoptosis may be induced on pathological tissues, but that it was unlikely that the mechanism involved was Fas-mediated. See page 556, lines 6-8. As such, the involvement of Fas-mediated apoptosis in the pathology was highly controversial at the time of the invention.

Further, Takiya et al. (1995) discussed on page 6 of the January 15, 2004 response supports that the expression of Fas does not correspond to TUNEL activity.

Also attached hereto is an abstract of an article by Ballardini et al., *Dig. Liver Dis.* 33:151-156 (2001), which supports that increased Fas expression does not necessarily lead to apoptosis. While Ballardini et al. published after the invention, the article still supports that the field is unpredictable and that there is not necessarily a direct correlation between Fas expression and apoptosis. That fact was true at the time of the invention and remained true in 2001. This is probative of the unpredictability of the invention.

One skilled in the art would therefore have no expectation of success or be motivated to achieve the invention from the teachings of the prior art. The present invention is therefore not obvious over the cited references and withdrawal of the rejection is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, PhD. (Reg. No. 40,069) at the telephone number below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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GMM/MAA
1110-0279P

Attachment: Ballardini et al., *Dig. Liver Dis.* 33:151-156 (2001) (Abstract only)

1: Dig Liver Dis. 2001 Mar;33(2):151-6. Related Articles, Links

Comment in:
- Dig Liver Dis. 2001 Mar;33(2):122-4.

Bile duct cell apoptosis is a rare event in primary biliary cirrhosis.

Ballardini G, Guidi M, Susca M, Ghetti S, Grassi A, Lari F, Fusconi M, Zauli D, Bianchi FB.

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BACKGROUND: The frequency of apoptosis in bile duct cells of primary biliary cirrhosis is still unclear spanning from rare to 50% in the various reports. AIM: To study bile duct cell apoptosis in stage I primary biliary cirrhosis lesions. PATIENTS: Nine stage I-II biopsies with a total number of 26 bile ducts of different sizes, selected from a larger series on the basis of the expression on serial frozen sections of HLA-DR and Fas antigens. METHODS: Apoptosis was evaluated by a DNA fragmentation assay on frozen sections, according to the manufacturer's protocol and by expression of apoptosis related cytokeratin neoepitopes. Bile duct cell proliferation was assessed by MIB1 (Ki-67) expression. RESULTS: Apoptosis was frequently found in inflammatory cells of portal tracts and sinusoids. Apoptosis of hepatocytes was also systematically observed. Only 4 positive bile duct cells were found in 3 bile ducts from 3 biopsies. Quantitative evaluation was not attempted. Cholangiocyte proliferation was observed in the same ducts and occasionally in other biopsies. CONCLUSIONS: These data suggest that cholangiocyte death by apoptosis at the level of typical primary biliary cirrhosis lesions is a rare event, at least in early stages of the disease. The observed rate of proliferation was consistent with the rate of apoptosis.

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